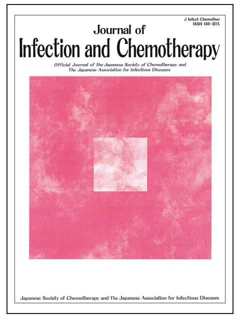


# Predictors of silent hypoxia in hospitalized patients with COVID-19 in Japan

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Note

Title: Predictors of silent hypoxia in hospitalized patients with COVID-19 in Japan

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Running title: Silent hypoxia in COVID-19 patients

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**Abstract**

**Introduction**

Silent hypoxia (SH) is common in patients with coronavirus disease (COVID-19) in Japan and other countries. Early identification of SH is important as more treatment options for COVID-19 have become available. This study aimed to identify predictors of SH using a nationwide COVID-19 registry of hospitalized patients.

**Methods**

Adult patients who were admitted to hospital with COVID-19 between January 2020 and June 2021 and who were hypoxic on admission ($SpO_2$: 70–94%), not transferred from another facility, and who did not have disturbance of consciousness, confusion, or dementia, were included. SH was defined as hypoxia in the absence of shortness of breath/dyspnea upon admission. Predictors of SH were identified using univariable and multivariable logistic regression.

**Results**

The study included 1,904 patients, of whom 990 (52%) satisfied the criteria for SH. Compared to patients without SH, patients with SH were older, more likely to be female, and had a slightly higher $SpO_2$ on admission. Compared to patients without SH, patients with SH had a lower prevalence of chronic lung disease (CLD) other than chronic obstructive pulmonary disease (COPD), asthma, and obesity. Multivariable analysis revealed that the independent predictors of SH were older age, a shorter interval from symptom onset to admission, higher $SpO_2$, and an absence of CLD or COPD.

**Conclusions**

The absence of underlying lung disease and older age were important predictors of SH. The results of this study, which is the largest such study reported to date in Japan, may help clarify the mechanism of SH.

Keywords: silent hypoxia, COVID-19, infection

Silent hypoxia (SH), also known as happy hypoxia, has been frequently observed in COVID-19 patients Japan and other countries [1-4]. The early identification of SH and initiation of therapeutic interventions are important given that more treatment options for coronavirus disease-2019 (COVID-19) have now become available. This study was conducted to identify the predictive factors for SH using the nationwide COVID-19 registry of hospitalized patients (COVIREGI-JP).

The patients who fulfilled the following criteria were included in the analysis: (1) ≥ 20 years of age, (2) no oxygen usage on admission, (3) 70% < $SpO_2$, < 94% on room air, (4) no disturbance of consciousness (AVPU scale: alert or verbal), (5) no confusion or dementia, and (6) not a transferred patient. SH was defined as the absence of shortness of breath (SOB)/dyspnea upon admission. The data of patients, admitted between January 2020 and June 2021, which were fixed by September 30, 2021, were used as previously described [5]. All analyses were performed using IBM SPSS 25. Univariable and multivariable analyses were performed using logistic regression, and independent predictors for the silent hypoxia were identified. Two–sided P value of < .05 was considered statistically significant. This study was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-004147-00).

The study included 1,904 patients, of whom 990 (52%) satisfied the criteria for SH. In univariable analysis, compared to the non-SH group, the SH group had more female and older adult patients (Table). Alcohol consumption was more prevalent in the non-SH group than in the SH group. The patients from the SH group had a slightly higher $SpO_2$ on admission, as well as a slightly lower temperature and heart rate than those in the non-SH group. The prevalence of chronic lung disease (CLD) other than chronic obstructive pulmonary disease (COPD), asthma, and obesity, was lower in the SH group than in the non-SH group. The days from symptom onset (DSO) were shorter in the SH group than in the non-SH group. Multivariate analysis revealed that the independent predictors of SH were older age, shorter DSO, higher $SpO_2$, and not having CLD or COPD.

The results were partially similar to those in the study by García-Grimshaw *et al*., which identified DSO as a predictor of SH [6]. However, they were not concordant with the report by Alhusain *et al.*, which did not include DSO or vitals on admission [7]. Both studies used different definitions of hypoxia and included symptoms as predictors. In the present study, although symptoms were excluded to avoid confounding effects, more comorbidities were considered. The correlation between the risk factors for severe COVID-19 and the predictors of SH was minimal [8].

Based on our results, patients with COPD and CLD were more likely to complain of SOB. Oxygen-requiring patients on admission were not included in the study; therefore, patients with advanced COPD or CLD were likely excluded. These findings suggest that patients with underlying pulmonary diseases that are not sufficiently advanced for them to be accustomed to hypoxia, are less likely to develop SH because they tend to be more aware of their respiratory status.

Various hypotheses regarding the pathomechanism of SH have been proposed [9-11]. The lung perfusion, sensory feedback, and central neural regulation of breathing are likely to be affected in patients with underlying lung abnormalities. The findings of the present study require further basic investigation and validation in non-Japanese cohorts.

Limitations of this study include the use of registry data, which may have resulted in selection bias, as previously reported [5]. Although we performed multivariable analysis, there may be some residual confounding.

In conclusion, in a large cohort of patients hospitalized with COVID-19, the absence of underlying lung disease and age were important predictors of SH. The results of this study, which included the largest number of reported cases, may help clarify the mechanism of SH.



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**Table. Predictors for silent hypoxia on admission among hypoxic COVID-19 patients**

| Parameters | Silent Hypoxia[a] (n=990) | Non–Silent Hypoxia[a] (n=914) | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | OR | P value[b] | OR | P value[b] |
| **Demographics** | | | | | | |
| Age (years), median (IQR) | 71 (60–80) | 65 (54–76) | 1.02 (1.02-1.03) | **<0.001** | 1.02 (1.01-1.03) | **0.002** |
| Male sex | 617 (62.3%) | 663 (72.7%) | 0.62 (0.51–0.75) | **<0.001** | 0.8 (0.58–1.11) | 0.179 |
| Japanese race | 950 (97.2%) | 870 (96%) | 1.46 (0.88–2.42) | 0.147 | 1.5 (0.74–3.05) | 0.258 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Current or previous smoker | 429 (51.5%) | 434 (54.5%) | 0.89 (0.73–1.08) | 0.232 | 1.01 (0.76–1.35) | 0.93 |
| Alcoholic beverage drinker | 382 (51.8%) | 406 (57.5%) | 0.8 (0.65–0.98) | 0.031 | 1.02 (0.76–1.36) | 0.92 |
| Days from symptom onset, median (IQR) | 6 (3–8) | 6 (4–9) | 0.93 (0.91-0.96) | **<0.001** | 0.94 (0.91–0.98) | **0.001** |
| **Vital signs on admission** | | | | | | |
| $SpO_2$, median (IQR) | 92 (91–93) | 91 (89–93) | 1.16 (1.12-1.2) | **<0.001** | 1.14 (1.09–1.19) | **<0.001** |
| Temperature in Celsius, median (IQR) | 37.4 (36.8–38.1) | 37.5 (36.9–38.3) | 0.88 (0.8-0.97) | **0.007** | 1.06 (0.92–1.22) | 0.392 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Respiratory rate, median (IQR) | 20 (17–22) | 21 (18–24) | 1.00 (1.00-1.00) | 0.512 | 1.00 (1.00–1.00) | 0.551 |
| Heart rate, median (IQR) | 89 (80–101) | 92 (82–103) | 0.99 (0.98-0.99) | **<0.001** | 1.00 (0.99–1.01) | 0.472 |
| **Comorbidities[c]** | | | | | | |
| Myocardial infarction | 33 (3.3%) | 32 (3.5%) | 0.95 (0.58–1.56) | 0.84 | 1.00 (0.46–2.14) | 0.992 |
| Congestive heart failure | 41 (4.1%) | 24 (2.6%) | 1.6 (0.96–2.67) | 0.071 | 1.78 (0.79–4.02) | 0.168 |
| Peripheral vascular disease | 18 (1.8%) | 23 (2.5%) | 0.72 (0.39-1.34) | 0.296 | 0.43 (0.15–1.26) | 0.125 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cerebrovascular disease | 86 (8.7%) | 55 (6%) | 1.49 (1.05–2.11) | 0.027 | 1.14 (0.66–1.98) | 0.64 |
| Chronic lung disease (excluding COPD) | 23 (2.3%) | 41 (4.5%) | 0.51 (0.3–0.85) | **0.010** | 0.27 (0.11–0.66) | **0.004** |
| COPD | 50 (5.1%) | 62 (6.8%) | 0.73 (0.5–1.07) | 0.11 | 0.35 (0.18–0.68) | **0.002** |
| Asthma | 42 (4.2%) | 65 (7.1%) | 0.58 (0.39–0.86) | **0.007** | 0.67 (0.39–1.16) | 0.154 |
| Liver disease | 33 (3.3%) | 29 (3.2%) | 1.05 (0.63–1.75) | 0.844 | 1.08 (0.48–2.43) | 0.85 |
| Peptic ulcer disease | 11 (1.1%) | 7 (0.8%) | 1.46 | 0.439 | 1.29 | 0.738 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (0.56–3.77) | | (0.3–5.58) | |
| Diabetes mellitus | 271 (27.4%) | 269 (29.4%) | 0.9 (0.74–1.1) | 0.32 | 0.85 (0.63–1.16) | 0.303 |
| Obesity[d] | 71 (7.2%) | 105 (11.5%) | 0.6 (0.43–0.82) | **0.001** | 0.98 (0.64–1.51) | 0.927 |
| Severe renal dysfunction | 17 (1.7%) | 9 (1%) | 1.76 (0.78–3.96) | 0.174 | 3.46 (0.69–17.25) | 0.13 |
| Solid tumors | 51 (5.2%) | 47 (5.1%) | 1 (0.67–1.51) | 0.993 | 0.65 (0.33–1.27) | 0.205 |
| Metastatic solid tumors | 17 (1.7%) | 15 (1.6%) | 1.05 (0.52–2.11) | 0.897 | 0.75 (0.27–2.14) | 0.594 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Leukemias or lymphomas | 6 (0.6%) | 10 (1.1%) | 0.55 (0.2–1.52) | 0.251 | 0.36 (0.07–1.86) | 0.221 |
| Collagen disease | 16 (1.6%) | 20 (2.2%) | 0.73 (0.38–1.43) | 0.362 | 0.65 (0.23–1.84) | 0.415 |
| Hypertension | 465 (47%) | 401 (43.9%) | 1.13 (0.95–1.36) | 0.175 | 1.01 (0.76–1.35) | 0.936 |
| Dyslipidemia | 222 (22.4%) | 218 (23.9%) | 0.92 (0.75–1.14) | 0.461 | 1.05 (0.77–1.44) | 0.758 |

[a]Presented as number (%) unless otherwise indicated. [b]Two–sided P value of < 0.05 was considered statistically significant (indicated as bold text). [c]Definitions were based on their Charlson Comorbidity Index scores, unless otherwise specified [12]. [d]Based on the physician's diagnosis. Abbreviations. COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OR, odds ratio.